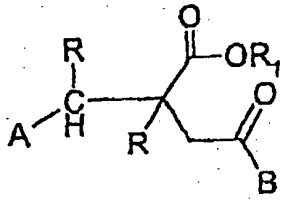
USE OF SUCCINIC ACID DERIVATIVES IN PRODUCING A MEDICAMENT INTENDED FOR THE TREATMENT OF INFLAMMATION

A subject-matter of the present invention is the use of succinic acid derivatives, disclosed in Patent EP 0 507 534, in the preparation of a medicament intended for the treatment of inflammation.

Thus, a subject-matter of the present application is the use of succinic acid derivatives corresponding to the general formula (I):



(I)

in which:

A represents a phenyl group optionally substituted by one, two or three substituents chosen from a halogen or a C_{1-6} alkyl or C_{1-6} alkoxy group; a thienyl, furyl or pyridyl or a cycloalkyl having from 3 to 8 carbon atoms;

B represents [lacuna] aminobicyclic group which consists of a 5- or 6-membered cyclic amino compound condensed with a 5- or 6-membered cycloalkyl ring which can have one or two unsaturated bonds, with the condition that B is bonded to the carbon atom of the

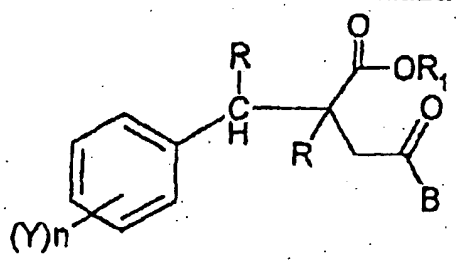
carbonyl group on the nitrogen atom; each R represents a hydrogen atom or the R residues are combined together to form a chemical bond; R_1 represents a hydrogen atom, a C_{1-6} alkyl group or an aralkyl group having from 7 to 10 carbon atoms; when there are geometrical isomers, each geometrical isomer, its E isomers and its Z isomers, its cis isomers and its trans isomers.

The compounds of general formula (I) can comprise one or more asymmetric carbon atoms. They can thus exist in the form of enantiomers or of diastereoisomers. The use of these enantiomers or diastereoisomers, and their mixtures, including racemic mixtures, forms part of the invention.

The compounds of general formula (I) can be provided in the form of the free base or of addition salts with pharmaceutically acceptable acids, as disclosed in EP 0 507 534. The use of these salts forms an integral part of the present invention.

In the present application, halogen represents an iodine, chlorine, bromine or fluorine atom.

More particularly, the use of succinic acid derivatives as defined below of formula (I):



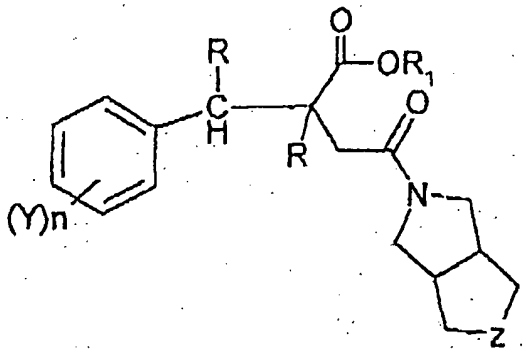
(I)

in which:

B represents [lacuna] aminobicyclic group which consists of a 5- or 6-membered cyclic amino compound condensed with a 5- or 6-membered cycloalkyl ring which can have one or two unsaturated bonds, with the condition that B is bonded to the carbon atom of the carbonyl group on the nitrogen atom; each R represents a hydrogen atom or the R residues are combined together to form a chemical bond; R_1 represents a hydrogen atom, a C_{1-6} alkyl group or an aralkyl group having from 7 to 10 carbon atoms;

Y represents a hydrogen atom, a halogen or a C_{1-6} alkyl or C_{1-6} alkoxy group and n represents 1, 2 or 3; is preferred.

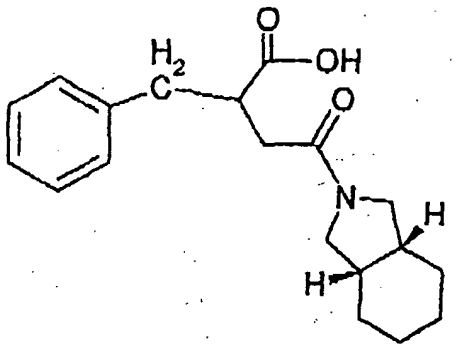
Among the latter, the preferred compounds are of formula (I):



(I)

in which Z represents an ethylene group or a vinylene group.

More specifically, the use of 2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid of formula



(I)

and more particularly of (S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid is preferred.

The compounds of the invention have been subjected to biological tests intended to demonstrate their anti-inflammatory activity.

The *in vivo* activity of the compounds of the present invention were studied in an experimental model of plantar inflammation in rats.

Inflammatory oedema of the paw of rats induced by the intradermal injection of carrageenan (CAR) (1% v/v) is produced and evaluated according to the method of Winter C.A. and Risley E.A. (Carrageenan-induced edema in the hindpaw of rats as an assay for anti-inflammatory drugs. Proc. Soc. Axp. Biol. Med., 19632, 11, 544-547).

The compounds of the invention are given orally 1 hour before the injection of CAR. A 1% solution of CAR in a saline solution is injected by the s.c. route into the subplantar part of the right hind paw of rats.

The volume resulting from the inflammatory

reaction is measured by plethysmography after 1.5, 3 and 4.5 hours from the injection of CAR.

The compounds of the invention at doses of between 0.5 and 10 mg/kg by the oral route confer lasting inhibition of the inflammation induced (between 1.5, 3 and 4.5 hours after the injection of CAR) of the order of 20 to 90% with respect to the control. Preferably, the compounds of the invention exhibit at doses of 10 mg/kg inhibition of the inflammation of the order of 50 to 90%.

The results show that the compounds of the invention exhibit anti-inflammatory properties *in vivo*. They can thus be used in the symptomatic treatment of painful conditions of light to moderate intensity and/or feverish states, more particularly in diabetic neuropathies, polyarthritis, arthrosis, lumbago, traumatological pain and inflammation in the ENT field.

The compounds of the invention can be presented, in combination with any appropriate excipient, in any form suitable for administration via the oral or parenteral route, for example in the form of tablets, gelatin capsules, sugar-coated tablets or oral or injectable solutions, as defined in EP 0 507 534.

The compounds of the invention can be administered at daily doses of between approximately 1 and 100 mg in adults by the oral route or between

approximately 0.1 and 100 mg by the parenteral route.